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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,469	11/01/1999	DAVID M. ARMISTEAD	VPI/95-09-DI	8756

7590

09/09/2004

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/431,469	ARMISTEAD ET AL.	
Examiner	Art Unit	
Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-25 and 31-56 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-25 and 31-56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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In the interview of 7/23/04, it was indicated that another supplementary amendment would be filed. The examiner stated that if such an amendment were quickly filed (i.e. within about two weeks of the interview), the amendment would be entered and she would grant another interview to discuss the new amendment. A proposed amendment was filed by fax on 7/26/04. On the same day, the examiner called Ms. Su to remind her that communications faxed directly to an examiner are informal communications, and to ask whether a formal amendment would be filed. Ms. Su said that it would be. At that time, the examiner reiterated that she would grant an interview upon filing of a formal amendment. As the telephone call did not concern the merits of the case, no Interview Summary was mailed. Applicant is hereby reminded that communications faxed directly to an examiner are considered INFORMAL communications and will not necessarily be entered into the record. No formal amendment has been entered as of the date of this office action.

Information Disclosure Statement

The IDS's files 10/3/03 and 2/24/04 have been considered in full.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-32, 37-48 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Producing a crystal of a molecule or molecular complex comprising amino acids 5-168 of CnA and 24-370 of CnB is new matter, as recited in claims 31 and 32, amended 2/9/04 and in claims 37-44, added in the amendment 4/23/04. Original claim 6 recited a crystal and preparation of a crystal comprising residues 17-392 of CnA complexed with CnB, FKBP12 and FK506. The originally filed specification, on page 12, discloses a complex comprising amino acids 17-392 of CnA, amino acids 5-169 of CnB, complexed with FKBP12 and FK506. The Example on pages 30-31 discloses production of a crystal comprising residues 17-392 of CnA, residues 1-169 of CnB, and the entirety of FKBP12 and FK506. Nowhere do the originally filed specification or claims recite or disclose a crystal, or production of a crystal comprising residues 5-168 of CnA and/or residues 24-370 of CnB, as recited in the amended claims. In the response filed 2/9/04, applicant points to pages 24-27 of the specification and to Figure 1 for support for the newly added limitations; however, none of these pages or Figure 1 provides support for a complex comprising the amino acids residues newly recited in the claims. For these reasons, claims 31-32 and 37-44 recite new matter.

A hydrophobic moiety which makes Van der Waals contact with, or forms a hydrogen bond with, "all or part of" specific amino acid residues of CnA or a homologue thereof, as recited in claims 45-47 and 50-51, added in the amendment of 4/23/04, is new matter. The original claims did not recite any limitations with regard to Van der Waals contacts or hydrogen bonding. The originally filed specification, on page 42, discloses that a linker may form Van der Waals contact or hydrogen bonds with *one or*

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more specific residues of FKBP12 or CnA. The specification is silent with regard to whether the Van der Waals interactions or hydrogen bonding takes place with the entirety of each residue (all) or with only a portion (part) of each residue (i.e. specific atoms). A disclosure for contact/bonding with *one or more* residues is not generally regarded in the art as being the same or equivalent to a disclosure for contact with "all or part of" a specific amino acid. As neither the originally filed specification or claims provide support for Van der Waals contact or hydrogen bonding between a hydrophobic moiety and either "all" or a "part of" any one of the recited amino acid residues of FKBP12 and/or CnA, the claims recite new matter.

Linkers of 7-11 , or 8-12 , which are limited to project a hydrophobic moiety from the center of a hydrophobic core, as recited in claims 45-48, added in the amendment of 4/23/04, is new matter. The original claims did not recite any limitations of linkers. The originally filed specification, on page 42, discloses a compound with a hydrophobic binding core comprising a "second linker" which projects a 7-11 moiety from the center of the binding core. The originally filed specification, on page 42, also discloses that the hydrophobic binding core may comprising a "third linker" which projects a 8-12 moiety from the center of the binding core. The specification is silent as to whether the second or third linker or any moiety of a second or third linker is hydrophobic. It is noted that while the overall binding core may be hydrophobic, individual portions thereof are not necessarily hydrophobic. It is well-known in the art that compounds may comprise hydrophobic and hydrophilic regions or residues, yet display "overall" hydrophobic characteristics. As neither the originally filed claims or specification provide support for a linker of 7-11 which projects a *hydrophobic moiety*, the claims recite new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-20, 25, 31, 33-35, and 37-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 each limits a chemical entity to comprise a "surrogate for a phosphate residue." The specification provides literal support for this limitation on page 43, but does not define a "surrogate" for a phosphate anywhere and there does not appear to be a single art-recognized definition for this term. As one skilled in the art would not know what limitation is intended by applicant for a "surrogate for a phosphate residue", the claims are indefinite.

Claims 37-40 recite the phrase "said binding pocket" in steps (c) and (e). It is unclear what the antecedent basis for this phrase is intended to be; i.e. the CnA (or CnA/CnB) binding pocket or a homologue binding pocket, therefore the claims are indefinite.

Claims 37-40 recite the phrase "said structure coordinates defining all or part of a binding pocket" in step (d). There is insufficient basis for this phrase in the claims, therefore the claims are indefinite. Step (c) of each claim recites a step of identifying a binding pocket, but nowhere do the claims recite either defining or identifying **structure coordinates** for a binding pocket, therefore there is no antecedent basis for the phrase.

Claims 45 and 47 each limit a linker to project a "second hydrophobic moiety" in line 4. As no "first" hydrophobic moiety is recited in the claims, it is unclear what is

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intended by the limitation of a "second" hydrophobic moiety, and the claims are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-25, 33-36, and 45-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over HENDRY et al. (US 5,705,335).

Applicant's arguments filed 2/9/04 have been fully considered but they are not persuasive. In response to the argument that the claimed energy minimization and fitting/docking steps cause a change in the computer program itself, it is noted that the program instructions do not actually change in response to the docking, the steps merely generate new (comparison) data. It is again noted that the data does not materially change the program itself nor is the data itself changed. Contrary to applicant's

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arguments, the method claimed is not one of "building" an energy-minimized structure (e.g. by sequential addition of atoms, side-chains, etc.). The CLAIMED methods merely recite docking which "utilizes" energy minimization; i.e. rotating a structure to find the face that "fits" into a binding pocket with the lowest interaction energy. Both the data and program steps remain the same; the fitting operation and energy calculations may be performed on any set of data provided it is arranged in a format recognized by the program. The data is used for comparison (e.g. to other data representing a ligand), but is not actually transformed into a different data set.

HENDRY teaches a method to evaluate the ability of a chemical compound to associate with another (the "degree of fit" of binding to a pharmacophore) wherein a ligand is docked (fitting operation) into a binding site, and the results evaluated (col. 7, lines 9-24). HENDRY also teaches "outputting" results of his fitting method (Figures 1-4). HENDRY further teaches that compounds identified using a computer modeling/docking algorithm may be synthesized (col. 10, lines 17-21) and evaluated for binding in *in vitro* assays (col. 10, line 40-col. 11, line 64). HENDRY further teaches molecular modeling and energy calculations to perform his fitting operations (col. 6, lines 25-42, col. 11, line 65-col. 12, line 11 and col. 13, lines 19-31), and teaches fitting through visual inspection of 3D images on a computer screen (Figure 6, col. 6, lines 44-52, and col. 7, lines 9-24). HENDRY teaches that his method may be performed on different sets of compounds and teaches design and assembly of compounds which fit into his "binding pocket" (col. 21, lines 54-63 and col. 13, lines 40-64), thereby making obvious all of the steps of the claimed methods. It is noted that the structure coordinates recited in the claims are nonfunctional descriptive material as they do not impose a change on the processing steps used in the claimed methods. Algorithms to fit or dock a molecular entity into a binding site of a molecule or molecular complex are known in the

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art, as set forth above. A method of using a known algorithm for its known purpose does not become nonobvious merely because new data is available for analysis.

Nonfunctional descriptive material cannot render non-obvious an invention that would have otherwise been obvious. See *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983) and MPEP 2106. Applicant is also directed to the Trilateral Project WM4 Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims at:

http://www.uspto.gov/web/tws/wm4/wm4_3d/report.htm

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571)

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272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
9/2/04